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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/094,921	06/15/1998	HORST LINDHOFER	80309	9008

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EXAMINER
HOLLERAN, ANNE L

ART UNIT	PAPER NUMBER
1642	23

DATE MAILED: 11/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/094,921	LINDHOFER ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication app ars on th cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13-21,23,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 13-21, 23, 26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed on March 22, 2002 and June 10, 2002 are acknowledged. The amendment March 22, 2002 refers to references listed in a supplemental IDS. However, neither the references nor the IDS are in the file, and the transmittal form for March 22, 2002 amendment does not indicate that an IDS was submitted with the amendment.

2. The declaration of inventor Lindhofer filed under 1.132 (attached to the amendment file March 22, 2002) has been considered.

3. Claims 24, 25, and 28-30 were canceled.

Claims 1-8, 13-21, 23, 26 and 27 are pending and examined on the merits.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejection Withdrawn:

5. The rejection of claims 1-8 and 13-21 and 23-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

6. The rejection of claims 23-25 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendment.

7. The rejection of claims 1-8, 13-21, 24-26, and 28 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn upon further consideration.

Claim Rejections Maintained:

8. The rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S.Patent 5,911,987; issued June 15, 1999; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; issued Nov. 17, 1998; filed June 7, 1996) and further in view of Lindhofer et al (Lindhofer, H. et al, J. Immunology, 155: 219-225, 1995) is maintained for the reasons of record. This rejection is newly applied to claims 1-8, 13, 15, 16, 19-21, 23, and 26. Thus, **claims 1-8, 13, 15, 16, 19-21, 23, 26 and 27 are rejected under 35 U.S.C. 103(a)**.

Claim 1 is interpreted as drawn to methods of making a vaccine composition comprising isolated autologous tumor cells, treating the tumor cells to prevent survival and incubating the treated tumor cells with bispecific antibodies that bind to a T cell, bind to at least one antigen on a tumor cells and bind to an Fc receptor of Fc receptor-positive cells. The bispecific antibodies also have a various combination isotypes. Claim 2 specificies the Fc receptor as the Fcγ receptor I, II, or III. Claim 3 specifies that the antibodies bind to monocytes, macrophages, dendritic cells, natural killer cells or activated neutrophils by the Fcγ receptor I. Clam 4 specifies that the antibodies are capable of inducing tumor-reactive compelment-binding antibodies. Claim 5 adds

the limitation that antibodies be specific for CD3. Clam 6 adds the limitation that the antibodies elicit the CD40, CD80, CD86, ICAM-1 or LFA-4 antigens or the secretion of cytokines by Fc-receptor positive cells. Claim 7 adds the limitation that the cytokines secreted by Il-1, IL-2, IL-4, IL-6, IL-8, IL-12, or TNFα. Claim 8 adds the limitation that the bispecific antibody contains an anti-CD3 and an anti-tumor-associated antigen specificity. Claim 13 is drawn to a method for preparation of a vaccine from the tumor cell preparation. Claims 15 and 16 specify the duration of the incubation period. Claims 19 adds the limitation that the amount of tumor cells used in the method is 10^7 to 10^9 cells. Claim 20 adds the limitation that bispecific antibodies be added in tan amount of 2 –100 ug. Claim 21 specifies that the cell treatment procedure is limited to irradiation. Claim 23 is drawn to a method of treatment of cancer comprising injecting the vaccine preparation of 1. Claim 26 is drawn to a pharmaceutical composition that is prepared by the method of claim 1. Claim 27 is interpreted as drawn to methods using bispecific antibodies having a combination isotype of rat-IgG2b/mouse-IgG2a, rat-IgG2b/mouse-IgG2b or rat-IgG2b/mouse-IgG3.

Volker teaches a method of preparing a cellular vaccine from autologous tumor cells by isolating the tumor cells, freezing and thawing the isolated tumor cells (inactivating them), infecting the tumor cells with Newcastle Disease Virus to antigenized the tumor cells and incubating the tumor cells with a bispecific cell binding reagent that has a specificity for a Newcastle Disease virus antigen and has a specificity for a T-cell (col. 6, lines 58- col. 8, line 13). The amount of tumor cells used to prepare the vaccine is 10^7 cells. The incubation step with the bispecific cell bonding reagent last for 30 minutes. The cells may be treated with 200 Gy radiation. The bispecific cell bonding reagent may have specificity for CD3. The cell

bonding reagents may be made up of antibodies or fragments of antibodies. Volker also includes a step of injecting the cellular vaccine preparation intradermally using a 0.9x40ml cannula. Volker fails to teach a bispecific antibody that has a specificity for an Fc receptor. However, the usefulness of bispecific antibodies comprising an anti-Fc recepetor specificity in the treatment of cancer is well known in the art as taught by Deo (col. 11, lines 11-16). Deo also teaches that the Fc receptor-specific antibodies are useful for binding to Fc receptor bearing cells such as moncytes, macrophages, neutorphils and dendritic cells, which are cells that are involved in specific killing of target cells and presenting antigens to the immune system (col. 6, lines 13-18). Deo also teaches that the Fc receptor-specific antibodies are useful for presenting antigen to antigen-presenting cells of a patient (col. 9, lines 20-30). Deo discloses a specific embodiment of a bispecific antibody, H22, which contains an anti-FcγI receptor (col. 17, lines 60-67), and which possesses ADCC activity mediated through FcγI receptor binding. Neither Volker nor Deo teaches making vaccine preparations using combination isotype bispecific antibodies, or any of the combinations recited in the claims. However, Lindhofer teaches that rat/mouse combinations made using the quadroma technique result in a higher yield of functional bispecific antibodies and also teach that a rat/mouse combination isotype is easier to purify (see pages 219-221 and Figure 1). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of Volker with that of Deo and of Lindhofer to have made the claimed invention. One would have been motivated to combine the teachings of Lindhofer with that of Volker and Deo, because Lindhofer teaches the advantages of using rat/mouse combinations in purification of bispecific antibodies and in generating high yields of usable antibody product.

Applicant argues that the prior art fails to suggest the claimed invention, and presents arguments by attacking each reference individually. Applicant argues that Volker fails to suggest the claimed invention, because antegenizing with a virus is a necessary step in the method of Volker, and that the present claims and specification do not suggest such a step. However, the scope of the claims does not exclude such a step. Applicant argues that the preferred embodiments of Deo are the use of antibody fragments that contain Fc portions, whereas the claimed invention is drawn to methods using intact antibodies. However, Deo is cited to demonstrate that usefulness of antibodies comprising Fc regions is known in the art. Applicant argues that because Lindhofer teaches a method of antibody purification that takes advantage of the heterologous nature of a rat/mouse bispecific antibody, and does not teach using such a bispecific antibody to arm tumor cells, that Lindhofer fails to teach the claimed invention. This argument is not found persuasive because the advantages that Lindhofer teach with respect to purification and high yield would have motivated one of skill in the art to use the antibodies of Lindhofer. The reason for using a product taught in the prior art does not have to be the same as the reason presented in the specification. Thus, the prior art as a whole appears to teach the claimed inventions. Volker teaches arming tumor cells with antibodies that bind to an antigen present on tumor cells and to a T cell and Deo teaches arming tumor cells with antibodies that bind to a tumor antigen and to an Fc receptor. Thus, the combination of the references teaches one that arming tumor cells with antibodies that bind to both a T cell and to an Fc receptor would be useful for the treatment of cancer. Lindhofer teaches one of the specific examples of the bispecific antibodies and teaches advantages for using such a bispecific antibody.

9. Claims 1-8, 13, 14, 17-21, 23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honsik (U.S. Patent 4,844,893; published July 4, 1989) in view of Linhofer (supra).

Claims 1-8, 13, 14, 17-21, 23, 26 and 27 may be interpreted as drawn to methods of making a vaccine preparation that comprises activated peripheral blood mononuclear cells.

Honsik teaches a method of using bispecific antibodies for the preparation of ADCC competent peripheral blood mononuclear cells comprising incubating peripheral blood mononuclear cells with bispecific antibodies that bind to the Fc receptor, bind to a tumor cell antigen and also bind to T-cells. The peripheral blood mononuclear cells are then mixed with tumor cells.

Honsik fails to make vaccine preparations using combination isotype bispecific antibodies, or any of the combinations recited in the claims. However, Lindhofer teaches that rat/mouse combinations made using the quadroma technique result in a higher yield of functional bispecific antibodies and also teach that a rat/mouse combination isotype is easier to purify (see pages 219-221 and Figure 1). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of Honsik with that of Lindhofer to have made the claimed invention. One would have been motivated to combine the teachings of Lindhofer with that of Honsik, because Lindhofer teaches the advantages of using rat/mouse combinations in purification of bispecific antibodies and in generating high yields of usable antibody product.

10. Claims 14, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite because it depends from claim 1, which recites a step "c", but then changes step "c". Claim 14 should be rewritten either an independent claim, or a claim that excludes step "c" of claim 1, and includes a step "d" (and step "e"), where step "d" is a recitation of the changed step "c" of claim 1.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
November 3, 2002

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